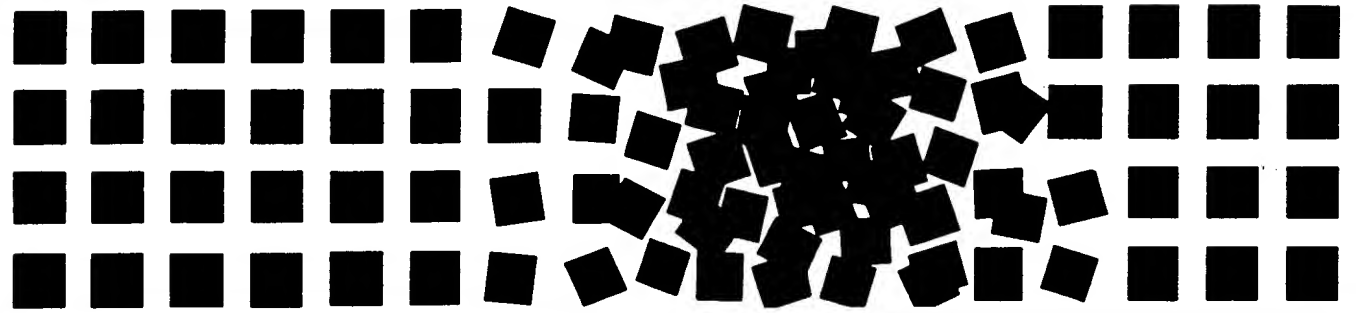
CANCER

Principles & Practice of Oncology



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DRUG DEVELOPMENT

Although there is an urgent need to move promising new therapies into clinical trial, important and clinically relevant information may be lost by proceeding immediately from a primary in vitro screen to a clinical trial without defining the in vivo activity of an agent, its pharmacokinetics and schedule dependency in animals, and its profile of toxicity for normal and malignant cells and tissues. Rather than omitting many of these important investigations, efforts should be made to better execute the studies in a timely manner to provide safe and reasonable starting doses for implementing phase I trials in patients.

Secondary in vitro studies to optimize the exposure time to an agent and to define its potential mechanism of action are useful for the investigators planning the in vivo studies. Examination of the dose-response data for several tumor cell lines should permit a selection of the optimal tumor system for subsequently evaluating in vivo efficacy. Further, preliminary pharmacologic studies in nontumor-bearing animals provide useful information about the plasma concentrations achievable and an estimate of the acute toxicity after systemic administration of a new agent. Success in identifying new therapies relies on the expeditious, yet careful, conduct of those studies pertinent to developing a promising in vitro observation (derived from either the cell-line screen or the molecular models) into an actual drug candidate.[45-48]

IN VIVO ANTITUMOR ASSAYS CURRENTLY IN USE

In the current NCI development schema, the human tumor cell line most sensitive to an active candidate in vitro is selected for testing as a xenograft in a subcutaneous implant site in a nude mouse.

Failure to demonstrate in vivo efficacy for agents that display strong in vitro evidence of antitumor activity should prompt additional studies to determine whether there is a pharmacokinetic or metabolic explanation for the loss of activity. The initial lead, either discovered by an empiric screen or as a result of rational chemical design, is rarely the optimal chemical entity for clinical investigation. Lead optimization and an iterative process between chemists and tumor biologists may be required to enhance the in vivo therapeutic index. Factors such as poor solubility and rapid in vivo metabolism may be corrected by analog development. More potent and less toxic derivatives can often be subsequently developed (i.e., provided the molecule is amenable to modification).

PRECLINICAL PHARMACOLOGY

Preclinical studies in mice, rats, and dogs provide essential information about pharmacokinetics and provide a basis for rational schedule development for the new drugs in humans. Factors such as bioavailability (for agents administered by the oral route), metabolism, renal excretion, and penetration into the central nervous system contribute to the understanding of how best to test a new drug in humans. Although there is no guarantee that the human subject will handle a new drug in the same way as the animal species, in most instances the major pathways for drug metabolism and excretion are qualitatively, if not quantitatively, the same across species.

Pharmacokinetic information in animals can also provide a rational basis for dose escalation in humans. Collins and associates have hypothesized that dose-limiting toxicity in mice and humans is a function of drug exposure, as measured by the area under the drug concentration in plasma × time curve (C × T).[49] They predict that animals and humans encounter dose-limiting toxicity at the same C × T for any given drug and that the experimentally determined dose-limiting C × T can be used as a target for dose escalation in humans. An analysis of recent experience with phase I drug trials suggested that for most, but not all, drugs, the relationship of C × T to toxicity holds across species.[49] This work potentially allows the clinical investigator to base initial dose escalation steps on measurements of C × T. Dose escalation can proceed in a more rapid fashion than formerly possible using empiric schemes, and wasteful multiple steps in dose escalation can be avoided. This approach, although apparently valid in retrospective studies, still requires broader validation in a prospective manner.

Drugs that demonstrate substantial interspecies variation in patterns of target tissue activation are not good candidates for this approach. For example, drugs activated by deoxycytidine kinase, such as fludarabine phosphate, are much more toxic to human marrow cells than to mouse bone marrow, because the enzyme concentration is higher in human cells.[50] In this instance, toxicity in humans would not be accurately predicted by the C × T approach. Furthermore, drug candidates that are excessively potent (e.g., several of the marine natural products) may have biologic effects at plasma concentrations lower than the level of reproducible detection. Consequently, those agents are not acceptable candidates for pharmacologically-guided dose escalation.

FORMULATION STUDIES

Although the preliminary pharmacologic and toxicologic studies may begin before a decision on the final formulation of a product, the IND-directed toxicology should be performed with the final formulation. In addition, other critical studies may be influenced by the formulation (e.g., bioavailability of an oral formulation, insolubility of an agent demonstrating interesting antitumor activity in the cancer screen). Three important factors that have an impact on formulation studies include solubility, stability, and dosage requirements.[51]

Because the route of drug administration for antineoplastic agents has primarily been through an intravenous approach, the solubility issue has provided a substantial challenge for a number of agents with limited aqueous solubility. Efforts to improve the solubility of an agent have primarily involved physical measures, including the use of various mixed solvent systems. Recently, novel approaches, including the use of micronization, liposomal encapsulation, and other unique delivery systems (e.g., cyclodextrins and coacervate systems) have been investigated in an effort to improve methods of drug delivery to tissues. Major efforts are needed to expand the vehicles that are available for intravenous drug delivery of agents with limited aqueous solubility and stability.

The prodrug approach uses chemical modification to solve the difficulty associated with drug insolubility. The most recent example of a simple prodrug approach was the synthesis of the monophosphate of 2-fluoro-adenine arabinoside (fludara-

bine).[52] In essence, the halogenated nucleoside was poorly soluble in aqueous solution. In contrast, the monophosphate (fludarabine) was more soluble and readily cleaved enzymatically in vivo to the 2-fluoro-adenine arabinoside. The nucleoside is rapidly rephosphorylated after transport to the intracellular compartment, and thus can be effective as an anticancer agent.[52]

Unique opportunities exist to use monoclonal antibodies to selectively deliver antineoplastic agents to targeted tumor cells. New methods of prodrug administration (e.g., ADEPT) are being evaluated that couple the administration of an anthracycline glucuronide and the use of a human β-glucuronidase conjugated to a monoclonal antibody for selected delivery to a tumor-bearing animal. It is hoped that this novel approach will enhance the selectivity of anticancer agents, and may have particular utility in the case of highly potent compounds.

TOXICOLOGIC INVESTIGATION

Preclinical toxicology is frequently the final step in the progression of a new chemotherapeutic drug from discovery to initial phase I testing in humans. The major objectives of the preclinical toxicologic studies include (1) the definition of the qualitative and quantitative organ toxicities (including dose and schedule dependencies); (2) the reversibility of these effects; and (3) the initial safe starting dose proposed for humans. In general, the best approach is to ensure the preclinical toxicologic studies reflect the intended clinical investigations in humans (i.e., identical formulation, schedules, and routes of drug administration, and dose levels anticipated to reflect the likely experience in patients).

The actual protocols for performing the preclinical toxicology at the NCI have changed dramatically during the last two decades.[53,54] Numerous schedules of drug administration were examined in a variety of animal species in the era before 1980. The emphasis later focused on mouse lethality studies for the initial dose-range–finding studies (i.e., LD_{10}, LD_{50}, and LD_{90}). The subsequent toxicologic studies were performed on fixed schedules to refine the doses associated with lethal and nonlethal toxicities. The preclinical toxicities reported correlated reasonably well with the subsequent clinical observations.[53,55–57] However, the extent of useless information relating to highly lethal murine doses (LD_{50} and LD_{90}) led to redesign of the toxicologic studies.

The current toxicologic investigations accepted by the Food and Drug Administration involve a simplified two-step approach. The initial step focuses on acute toxicity in small animals (e.g., mice), and the major endpoint is a determination of the LD_{10}, the dose that produces lethality in approximately 10% of the mice.

The subsequent second phase of preclinical toxicologic investigation is more extensive. The emphasis is given to a careful qualitative and quantitative characterization of the organ-specific toxicities in rodents associated with the schedule and route of administration that is to be used in the initial clinical trial. Attention is given to defining accurately those toxicities that are likely to be observed at doses slightly higher than the highest nontoxic dose. Careful investigation of the doses in the animals that approximate the highest projected tolerable dose in the model should provide data that are more relevant to the anticipated clinical experience in patients.

In the past, most new antineoplastic agents were tested clinically on two relatively fixed schedules of drug administration (i.e., single-bolus intravenous dose once every 3 to 4 weeks and 5 consecutive days of treatment repeated at 3- to 4-week intervals). The most frequently employed toxicologic protocols reflect each of these schedules. Some newer agents entering preclinical evaluation for cancer therapy are being proposed for continuous intravenous infusion or oral dosing. It is critically important that the preclinical toxicologic protocol simulates the planned therapeutic approach in patients.

Because there may be substantial variation between species in their tolerance to a drug, the safety of a projected starting dose in humans is confirmed by examining the preclinical toxicities in at least two species. Both the qualitative and the quantitative toxicities are usually well defined after investigation of a small animal model (e.g., mouse) and a larger animal (e.g., dog). Only occasionally is testing needed in an additional large animal (e.g., monkey), although this species may be useful for defining central nervous system pharmacokinetics.

Certain organ-specific toxicities are reliably detected with the current toxicologic models (e.g., myelosuppression and gastrointestinal toxicity). In contrast, hepatic and renal toxicities are often missed or falsely positive in animal testing. Toxicities involving the heart, lung, nervous system, pancreas, and integument are even less reliably appreciated. At best, the preclinical evaluation can establish a safe starting dose for humans and predict acute organ toxicity. A complete definition of the toxicologic profile of a new agent usually emerges only after extensive clinical experimentation.

CONCLUSION

The processes of drug discovery and development of anticancer agents involve substantial time, effort, and resources. The approaches to identify the new therapies are constantly being evaluated and modified. The strategies employed for drug discovery range from empiric screening (the source of most of the current active drugs) to carefully designed proposals to exploit the major advances in cancer biology. However, the process of testing a new agent and bringing it to clinical trial only begins with the discovery of a new active principle. Efficient development of new discoveries demands the cooperation of a multidisciplinary team of investigators who understand and respond to the urgent need for new cancer agents. The combined resources of government, academic, and the pharmaceutical industry laboratories are needed to be successful in dealing with the formidable task of finding effective new therapeutic products for cancer patients.

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